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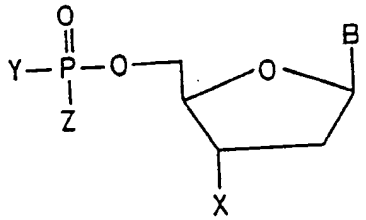

(I)

(57) Abstract

The present invention relates to nucleoside phosphate triesters and processes for their preparation. In particular, the present invention relates to nucleoside analogues of formula (I), where B = an organic base, X = -H or $-N_3$, Z = $-NR^1R^2$, and Y = $-OR^3$ or NR^4R^5, wherein R^1, R^2, R^3, R^4 and R^5 are the same or different and are selected from -H, alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups.

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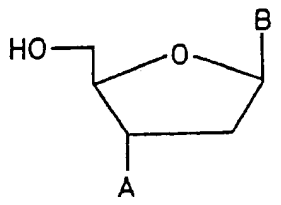
NUCLEOSIDE ANALOGUES

This invention relates to nucleosides and in particular to nucleoside phosphate triesters and processes for their preparation.

Nucleoside analogues of general formula (I) are currently of considerable interest for use as therapeutic agents in the treatment of viral infections and in particular acquired immunodeficiency syndrome (AIDS).



(I)

where A = H, or $-N_3$ and

B = a base such as adenine, thymine, guanine, or cytosine,

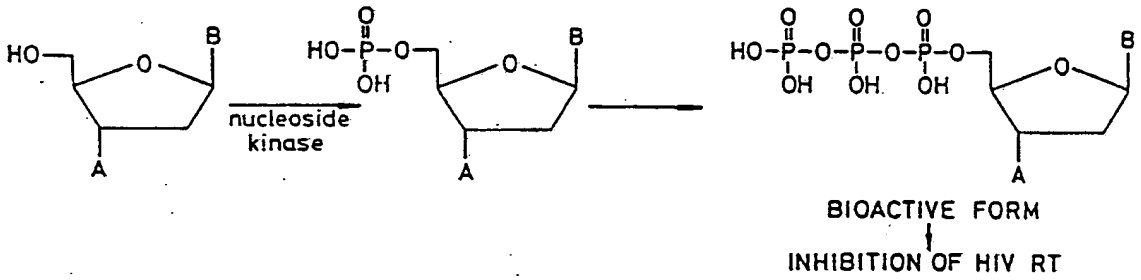
Particular examples include 2',3'-dideoxycytidine (ddC) (B = cytosine, A = H), 2',3'-dideoxyadenosine (ddA) (B = adenine, A = H), and 3'-azidothymidine (AZT) (B = thymine, A = N_3). AZT (Mitsuya et al., 1985) has found widespread clinical use as an inhibitor of human immunodeficiency virus (HIV) in the treatment of AIDS.

Other nucleoside analogues have found widespread use in the treatment of a number of viral infections; for example, 9-β-D-arabinofuranosyladenine (araA) in the treatment of herpes simplex encephalitis and disseminated herpes zoster (North et al.I, 1979).

AIDS was first recognised as a distinct clinical entity in 1981 (Gottlieb et al., 1981). The main target in anti-AIDS treatment has been the causative agent itself, the HIV virion. In particular, being a retrovirus, HIV depends on a unique viral enzyme, reverse transcriptase (RT), to proliferate. This enzyme has long been considered an attractive target for an attack on retroviruses (Smith et

al., 1974; Chandra et al., 1977).

The mode of action of AZT (Scheme I below) as an inhibitor of HIV in lymphocytes has been studied in detail (Furman et al., 1986). In common with other nucleoside analogues, AZT requires conversion to its 5' - triphosphate (Warqar et al., 1984; Cooney et al., 1986). Thus, following transport of the nucleoside across the cell membrane, the nucleoside is monophosphorylated by a nucleoside kinase enzyme present in the cell. Further kinase enzymes convert the monophosphate to the corresponding triphosphate product, which is the bioactive form. The bioactive form efficiently and selectively inhibits the HIV reverse transcriptase and its incorporation into DNA results in termination of DNA synthesis.



REACTION SCHEME I

Reaction Scheme I

However, nucleoside analogues suffer from a number of problems in relation to their anti-viral activity. First, the compounds are rapidly deactivated. For example, deactivation of nucleosides may occur by cleavage of the glycosidic bond by phosphorylase enzymes.

Phosphorylases are known to cleave the glycosidic bond in natural nucleosides (Stryer, 1981). Furthermore,

phosphorylases have been specifically implicated in the degradation of nucleoside analogues with therapeutic applications (Birnie et al., 1963; Saffhill et al., 1986).

In addition, where the base portion (B) of the nucleoside is adenine, guanine or cytosine, the nucleosides may be deactivated by deaminase enzymes. Deaminases cause the loss of the amine group from the base portion (B) of the nucleoside. For example, adenosine deaminase mediates in the deactivation of araA by converting it to arahypoxanthine (Bryson et al., 1976 and Haskell, 1977). In an effort to overcome this major problem, potent inhibitors of deaminase enzymes have been sought (Cha, 1976; Schaeffer et al., 1974). However, whilst the therapeutic effect of the nucleoside compounds may be improved in the presence of deaminase inhibitors (Agarwal et al., 1978; Sloan et al., 1977), the inhibitors themselves may have undesirable toxic side effects (North et al.II, 1979).

In an alternative approach to overcoming the problem of deactivation by deaminase enzymes, deamination resistant compounds have been sought. For example, a major substrate requirement of adenosine deaminase is a free 5'- hydroxyl group (Bloch et al., 1967). Many 5'- modified adenosine nucleosides have been prepared and are indeed resistant to adenosine deaminase (Declercq et al., 1977).

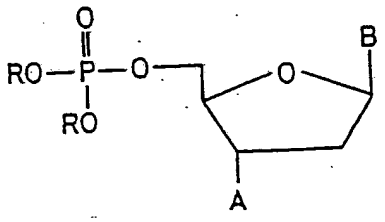
A second problem leading to poor clinical response to the nucleosides results from dependence on nucleoside kinases to effect monophosphorylation of the nucleoside. Poor intracellular phosphorylation may result in a poor clinical response to the nucleoside. In some cases a dependence on the virally-coded kinases is advantageous since it leads to enhanced antiviral selectivity (Furman et al., 1979). However, in most cases it is deleterious. There are now many reports of the absence, low activity or deletion of the kinase leading to a poor clinical response to the nucleoside analogue (Reichard P. et al., 1962; Morse P.A. et al., 1965;

and Bapat A.R. et al; 1983).

A further problem relating to the clinical use of nucleosides is their poor physical properties, in particular their low solubility in water and poor membrane penetrability.

The above-mentioned problems associated with nucleosides mentioned above have prompted investigation of bio-active phosphorylated nucleosides as chemotherapeutic agents in their own right. However, little, if any clinical benefit arises from the use of pre-formed monophosphate nucleosides in comparision to the corresponding nucleosides (Heidelberger C. et al., 1960). This is commonly attributed to poor membrane penetration of the charged monophosphate and the rapid extra-cellular cleavage to the corresponding nucleoside (Posternak, 1974; Lichtenstein. et al., 1960; Liebman et al., 1955).

More recently the use of uncharged phosphate triester nucleoside derivatives (II) as more lipophilic and therefore more membrane soluble pro-drugs of the nucleosides have been reported (Farquhar D. et al., 1983 and 1985; Hunston R.N. et al., 1984 and Chawla R.R. et al., 1984; Declercq et al., 1988). The therapeutic utility of such compounds is, however, disappointing.



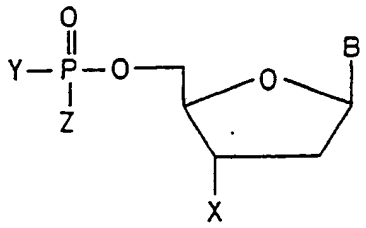
(II)

The triester compounds (II) show increased stability to deactivation by enzymes such as deaminases and may be expected to possess the desired lipophilicity to facilitate crossing of the cell membrane. However, once inside the

cell, in order to function as an HIV inhibitor according to Reaction Scheme I, the compounds require hydrolytic cleavage of the two 'R'-groups. It is postulated that the disappointing bio-activity of these compounds is a consequence of the cells, inability to effect such a hydrolytic cleavage. This is probably a consequence of the general lack of triesterase activity in cells.

There remains, therefore, a need for chemical compounds which fulfil the desired criteria of improved resistance to enzymatic deactivation, reduced kinase dependence and improved physical characteristics.

Accordingly, a first aspect of the present invention provides a nucleoside analogue of the formula:



Where B = an organic base

X =-H or-N_3

Z =-NR^1R^2

Y =-OR^3 or-NR^4R^5

R^1,R^2,R^3,R^4 and R^5 are the same or different and are selected from -H, alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl.

In such nucleoside analogues the base portion may be any organic base; for example, purine or pyrimidine bases. Preferably however, the base is adenine, thymine, guanine or cytosine. Most preferably the base is thymine.

When Y is not Z it will be appreciated that the phosphate group is an asymmetric chiral centre. Consequently the compound may be a single diastereomer or a mixture of diastereomers with respect to the phosphate chiral centre. The biological activity of the individual or mixed diastereomers may be different. Preferably the compounds of the present invention are single diastereomers. More preferably the compounds of the present invention are the most biologically active diastereomers. For example, diastereomers of 3'- azidothymidine- 5'-(ethylmethoxyvalinyl)- phosphate and 3'-azidothymidine - 5' - (hexylmethoxyvalinyl) - phosphate may be separated and shown to possess different degrees of biological activity.

-X may be selected from either -H or $-N_3$. Preferably X = $-N_3$.

The nucloside analogue of the present invention may be particularly useful in the treatment of AIDS.

The nucleoside analogues of the present invention have been shown in <u>in vitro</u> assays to be excellent inhibitors of HIV proliferation. Thus, an assay in which the nucleoside analogues of the present invention, suitable host cells, and HIV are incubated together, indicates that the IC_{50} of the compounds (i.e. concentration of the compound required to produce a 50% reduction in the formation of HIV antigen) is typically between 0.05 and 100 μM. Enhanced inhibition may be observed in an assay in which the compounds and host cells are preincubated prior to addition of HIV.

In particular it has been noted that while the nucleoside analogues of the present invention are excellent <u>in vitro</u> inhibitors of HIV proliferation the nucleoside analogues present low toxicity towards uninfected cells.

It is believed that the compounds of the present invention

overcome the above-mentioned problems associated with the bioactivity of nucleoside analogues in a number of ways. First, the compounds possess enhanced stability towards deactivation; second, the phosphorylated structure of the compounds leads to a reduced dependence on kinase enzymes to phosphorylate the nucleoside; and third, the uncharged nature of the compounds enables them to cross the lipophilic cell membranes.

In particular, it is postulated that once the uncharged compounds have been transported across the cell membranes the nitrogen-phosphorus amide bond is hydrolysed, possibly by protease enzymes. The resulting phosphate diester may then be further hydrolysed by, for example, diesterase enzymes, to yield the corresponding monophosphate. The monophosphate is then a substrate for transformation by kinase enzymes to the corresponding triphosphate, as shown in Reaction Scheme I. Thus, the bioactive form of the nucleoside is produced. It is not intended to limit this disclosure to this postulate explaining the surprisingly efficacious nature of the compounds of the present invention.

-Y may be $-OR^3$ or $-NR^4R^5$. Preferably, Y = $-OR^3$.

R^1,R^2,R^3,R^4 and R^5 are the same or different and are selected from hydrogen, alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups.

Preferably the alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups from which R^1,R^2,R^3, R^4 and R^5 may be selected comprise C_1 to C_{10} alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups. The groups may be branched or unbranched.

The groups from which R^1, R^2, R^4 and R^5 may be selected also include amino acids, oligopeptides and polypeptides.

Preferably, R^3 is a substituted alkyl group. More preferably, R^3 is a 2,2,2-trihaloethyl group, a 2,2-dihaloethyl group or a 2-haloethyl group. More preferably, R^3 is a 2,2,2-trichloroethyl group such that the compound of the present invention is a 2,2,2-trichloroethyl phosphate ester. In vitro assays have shown compounds of this type to be particularly effective inhibitors of HIV proliferation.

It will be appreciated that varying the individual substituents -X,-Y,-Z and -B enables the nucleoside analogue's properties to be tuned to the optimum combination for biological activity. For example, modification of the structure may enhance the selectivity of hydrolysis in the infected cell; the substituents may also be chosen to enhance the physical characteristics of the nucleoside analogue, for example to increase the lipophilicity and thereby enhance its transport across the cell membrane or to increase the solubility of the nucleoside analogue.

Preferably R^1 is hydrogen and $R^2 = -CHR^6CO_2R^7$ where R^6 and R^7 are the same or different and are selected from hydrogen, alkyl groups, aryl groups, acyl groups, substituted alkyl groups, substituted aryl groups and substituted acyl groups.

The groups from which R^7 may be selected include amino acids, oligopeptides and polypeptides.

It has been noted that small structural changes to R^2 and/or R^3 cause large variations in the biological activity of the nucleoside analogue.

Preferably the alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups from which R^6 and R^7 may be selected comprise C_1 to C_{10} alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups. The groups may be branched or unbranched.

Preferably R^6 may be selected from C_1 to C_3 alkyl groups. More preferably R^6 is methyl or iso-propyl.

Thus, in such compounds there is an amino acid portion (Z is $NHCHR^6CO_2R^7$) attached to the phosphate group. When R^6 is not hydrogen, the α -carbon atom to which R^6 is attached is an asymmetric centre.

Thus, diastereomers, corresponding to D- and L- amino acids, about the α-carbon atom may exist. The nucleoside analogue of the present invention may be single diastereomers or a mixture of diastereomers about the α-carbon asymmetric centre. Preferably, the nucleoside analogue of the present invention are single diastereomers. More preferably, the nucleoside analogue of the present invention is the most biologically active diastereomer.

Preferably the nucleoside analogue of the present invention has R^1 =-H

R^2 =-CHR^6CO_2Me

where R^6 =-$CHMe_2$
-CH_2Ph
-Me
-CH_2CHMe_2
-$CHMeCH_2Me$, and

R^3 = Me, Et, Pr, Bu, Hex, 2,2,2-trichloroethyl.

More preferably the nucleoside analogue of the present invention is selected from:

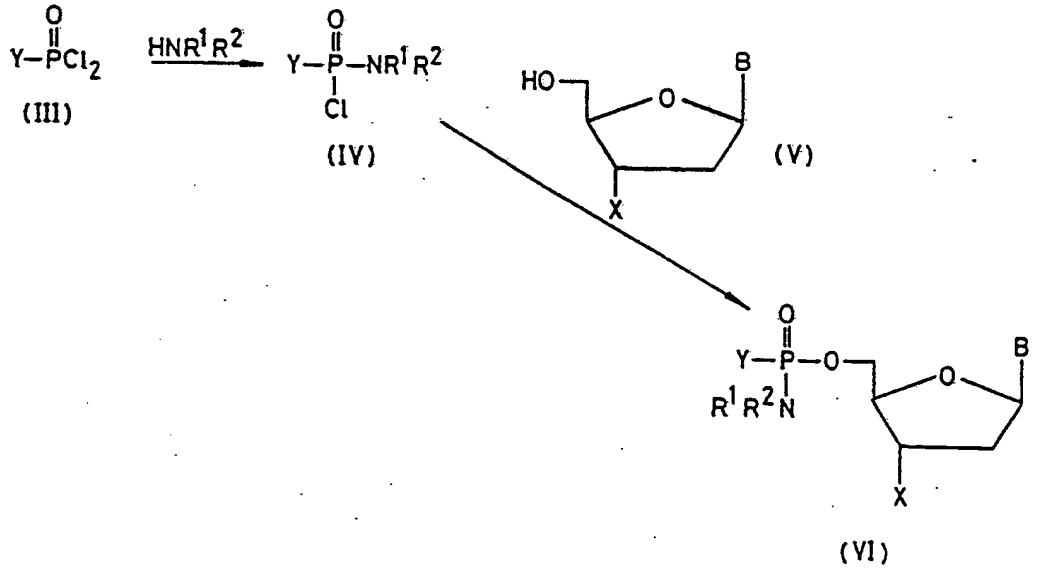
3'- azidothymidine-5'-(methylmethoxyvalinyl)- phosphate;
3'- azidothymidine-5'-(ethylmethoxyvalinyl) - phosphate;
3'- azidothymidine-5'-(propylmethoxyvalinyl)- phosphate;
3'- azidothymidine-5'-(butylmethoxyvalinyl)- phosphate;
3'- azidothymidine-5'-(hexylmethoxyvalinyl)- phosphate;
3'- azidothymidine-5'-(ethylmethoxyphenylalaninyl)-phosphate;

3'- azidothymidine-5'-(ethylmethoxyalaninyl)- phosphate;
3'- azidothymidine-5'-(ethylmethoxyleucinyl)- phosphate;
3'-azidothymidine-5'-(ethylmethoxyisoleucinyl) -phosphate;
3'-azidothymidine-5'-(2,2,2-trichloroethylmethoxyalaninyl) phosphate.

More preferably, the nucleoside analogue of the present invention is 3'-azidothymidine-5'-(2,2,2-trichloroethyl methoxyalaninyl) phosphate.

A second aspect of the present invention provides a process for the preparation of a nucleoside analogue according to the first aspect of the present invention.

The nucleoside analogue according to the first aspect of the present invention may be prepared according to the scheme outlined in Reaction Scheme II.



(III) (IV) (V) (VI)

Reaction Scheme II

Reaction of the phosphorodichloridate (III) with the amine HNR^1R^2 yields the aminophosphorochloridate (IV). Reaction

of the aminophosphorochloridate (IV) with a nucleoside yields a nucleoside monophosphate triester (VI) of the present invention.

The phosphorodichloridate (III) may be prepared by conventional means.

Preparation of the amino phosphorochloridate (IV) may be accomplished by reaction of the phosphordichloridate (III) and an amine (HNR^1R^2) under standard conditions (Van Boom et al., 1975; Michaelis, 1903). For example, by the dropwise addition of the amine (R^1R^2NH) to the phosphorodichloridate (III) in ether solution at -40°C followed by warming to ambient temperature.

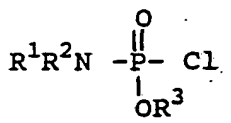
Alternatively, amino alkoxy phosphorochloridates (IV) where Y= OR^3, may be prepared by reaction of an alcohol (R^3OH) with an aminophosphorodichloridate ($R^1R^2NPOCl_2$) (Wolff et al., 1957).

Reaction of (IV) and (V) to give (VI) may be performed in pyridine as solvent. However, the reaction is slow. Preferably the reaction is performed in THF in the presence of N-methylimidazole.

Typically, the nucleoside (V) and 2 equivalents of aminophosphorochloridate (IV) are stirred together for 16 hours at room temperature in THF solution (5 ml/mmol) in the presence of 4 equivalents of N-methylimidazole. The nucleoside monophosphate triester (VI) may be isolated by a conventional extractive work up and chromatographic purification.

The reaction leading to preparation of the nucleoside monophosphate triesters (VI) may lead, when Y is not Z, to the formation of a mixture of diastereomers about the phosphate asymmetric centre. The diastereomers may be readily differentiated in their ^{31}P NMR spectrum.

A third aspect of the present invention comprises a chemical compound of the formula



where $R^1 = -H$

$R2 = -CHR^6CO_2R^7$

R^3, R^6, R^7 are the same or different and are selected from -H, alkyl, aryl, acyl, substituted alkyl, substituted acyl and substituted aryl groups.

Preferably, the alkyl, aryl, subsituted alkyl and substituted aryl groups from which R^3, R^6 and R^7 may be selected comprise C_1 to C_{10} alkyl, aryl, substituted alkyl and substituted aryl groups. The groups may be branched or unbranched.

More preferably, the third aspect of the present invention provides the compounds methylmethoxyvalinyl phosphorochloridate, ethylmethoxyvalinyl phosphorochloridate, propylmethoxyvalinyl phosphorochloridate, butylmethoxyvalinyl phosphorochloridate, hexylmethoxyvalinyl phosphorochloridate, ethylmethoxyalaninyl phosphorochloridate, ethylmethoxyphenylalaninyl phosphorochloridate, ethylmethoxyleucinyl phosphorochloridate, ethylmethoxyisoleucinyl phosphorochloridate, 2,2,2-trichloroethyl methoxyalaninyl phosphorochloridate.

A compound of the third aspect of the present invention may be prepared by reaction of an alkoxy phosphorodichloridate $R^3OP(O)Cl_2$ with an amino acid ester $H_2NCHR^6CO^2R^7$, for example, by the dropwise addition of the amino acid ester to the alkoxy phosphorodichloridate in ether solution at -40°C

followed by warming to ambient temperature.

A compound of the third aspect of the present invention may be used in the preparation of a nucleoside analogue of the first aspect of the present invention.

A fourth aspect of the present invention provides a pharmaceutical composition comprising a nucleoside analogue according to the first aspect of the present invention in association with a pharmaceutically acceptable excipient.

A fifth aspect of the present invention provides a nucleoside analogue according to the first aspect of the present invention in a form suitable for parenteral or oral administration.

A sixth aspect of the present invention provides a nucleoside analogue according to the first aspect of the present invention for use as a pharmaceutical.

A seventh aspect of the present invention provides a process for the preparation of a pharmaceutical composition comprising bringing a nucleoside analogue of the first aspect of the present invention into association with a pharmaceutically acceptable excipient.

An eighth aspect of the present invention provides a method of treatment comprising the administration, to a human or animal in need of such treatment, of an effective amount of a nucleoside analogue according to the first aspect of the present invention.

Preferably, the eighth aspect of the present invention provides a method of treatment of a viral infection. More preferably the viral infection is human immunodeficiency virus.

A ninth aspect of the present invention provides use of a

nucleoside analogue according to the first aspect of the present invention for the manufacture of a medicament for the treatment of a viral infection.

Preferably the viral infection is human immunodeficiency virus.

A tenth aspect of the present invention provides a pharmaceutically acceptable salt or addition compound of a nucleoside analogue according to the first aspect of the present invention.

The present invention will now be described by reference to specific embodiments.

Preparation of Methylmethoxyvalinyl phosphorochloridate

L-Valine methyl ester (1.50g, 11.4mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of methyl phosphorodichloridate (0.83g, 5.57mmol) in diethyl ether (10mL), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 17 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as a pale yellow oil (0.96g, 71%).

^{31}P nmr $\delta(CDCl_3)$ +16.12, +15.66.

^{1}H nmr $\delta(CDCl_3)$ 4.10 (m, 1H, NH), 3.78(d, 3H, CH_3OP), 3.60 (m, 4H, CH^*, valinyl OCH_3), 2.00(m, 1H, iPr CH), 0.90(d, 3H, valine CH_3), 0.75(d,3H, valine CH_3).

Preparation of Ethylmethoxyvalinyl Phosphorochloridate

L-Valine methyl ester (1.00g, 7.63mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of ethyl phosphorodichloridate (0.59g, 3.63mmol) in diethyl ether (10mL), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 2 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as a colourless gum (0.75g, 85%).

^{31}P nmr $\delta(CDCl_3)$ +14.06, +13.62.
^{1}H nmr $\delta(CDCl_3)$ 4.20 (m, 2H, CH_2 OP), 3.80 (m, CH*), 3.70 (s, 3H, OCH_3), 2.00 (m, 2H, NH, iPr CH), 1.30 (t, 3H, ethyl CH_3), 0.90 (d, 3H, valine CH_3), 0.70 (d, 3H, valine CH_3).

Preparation of Propylmethoxyvalinyl Phosphorochloridate

L-Valine methyl ester (0.93g, 7.12mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of propyl phosphorodichloridate (0.60g, 3.39mmol) in diethyl ether (10ml), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 16 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as a pale yellow oil (0.90g, 98%).
^{31}P nmr $\delta(CDCl_3)$ +13.75.
^{1}H nmr $\delta(CDCl_3)$ 4.00 (m,3H, CH_2OP, NH), 3.65 (m, 4H, CH*, OCH_3), 2.00 (m, 1H, iPrCH), 1.65 (m, 2H, CH_3 $C\underline{H}_2$), 0.75-0.90 (m,9H, valine CH_3, $C\underline{H}_3$ CH_2).

Preparation of Butylmethoxyvalinyl Phosphorochloridate

L-Valine methyl ester (0.86g, 6.59mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of butyl phosphorodichloridate (0.60g, 3.14mmol) in diethyl ether (10mL), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 16 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as pale yellow oil (0.88g, 98%).
^{31}P nmr $\delta(CDCl_3)$ +14.28, +13.75.
1H nmr $\delta(CDCl_3)$ 4.10(m, 2H, CH_2OP), 3.75(m, 4H, CH*,OCH_3), 3.50 (m, 1H, NH), 2.00 (m, 1H, iPr CH), 1.70 (m, 2H $C\underline{H}_2CH_2OP$), 1.35 (m, 2H, CH_3 $C\underline{H}_2$), 0.80-1.00(m, 9H, valine CH_3, $C\underline{H}_3CH_2$).

Preparation of Hexylmethoxyvalinyl Phosphorochloridate

L-Valine methyl ester (1.14g, 8.69mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of hexyl phosphorodichloridate (0.86, 4.14mmol) in diethyl ether (10mL), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 16 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as a pale yellow oil (1.25g, 96%).

^{31}P nmr $\delta(CDCl_3)$ +14.40, +13.67.

^{1}H nmr $\delta(CDCl_3)$ 4.30 (m, 1H,NH), 4.10 (m, 2H, CH_2 OP), 3.60 (m, 4H, CH*, OCH_3), 2.00 (m, 1H, iPr CH), 1.60 (m, 2H, $C\underline{H}_2CH_2OP$), 1.20 (m, 6H, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 0.80-0.90 (m, 9H, valine CH_3, $C\underline{H}_3CH_2$).

Preparation of Ethylmethoxyalaninyl Phosphorochloridate

L-Alanine methyl ester (2.42g, 23.5mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of ethyl phosphorodichloridate (1.82g, 11.2mmol) in diethyl ether (10mL), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 3 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as a pale yellow oil (1.95g, 78%).

^{31}P nmr $\delta(CDCl_3)$ +10.97, +10.85.

^{1}H nmr $\delta(CDCl_3)$ 3.90 (m, 2H, CH_2OP), 3.75-3.80 (m, 4H, OCH_3, CH*), 3.60 (m, 1H, NH), 1.80 (d, 3H, alanine CH_3), 1.30 (t, 3H, ethyl CH_3).

Preparation of Ethylmethoxyphenylalaninyl Phosphorochloridate.

L-Phenylalanine methyl ester (0.36g, 2.00mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of ethyl phosphorodichloridate (0.15g, 0.91mmol) in diethyl ether (10mL), at -40°C. The

reaction was allowed to warm to ambient temperature, with stirring for 4 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as a colourless oil (0.27g, 96%).

^{31}P nmr $\delta(CDCl_3)$ +10.97, +10.89.

^{1}H nmr $\delta(CDCl_3)$ 7.15 (s, 5H, Ph), 5.10 (d, 2H, $PhC\underline{H}_2$), 3.85 (m, 2H, CH_2OP), 3.60 (m,4H, OCH_3, CH^*), 3.40 (m, 1H, NH), 1.40 (t, 3H, ethyl CH_3).

Preparation of Ethylmethoxyleucinyl Phosphorochloridate

L-Leucine methyl ester (2.00g, 13.8mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of ethyl phosphorodichloridate (1.07g, 6.56mmol) in diethyl ether (10mL), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 3 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as a pale yellow oil (1.71g, 96%).

^{31}P nmr $\delta(CDCl_3)$ +11.27, +10.85.

^{1}H nmr $(CDCl_3)$ 4.20 (m, 2H, CH_2OP), 3.85 (m, 1H, CH^*), 3.70 (s, 3H, OCH_3), 3.40 (m, 1H, NH), 1.70 (m, 1H, i-Pr CH), 1.5-1.6 (m, 2H, leucine CH_2), 1.35 (t, 3H, ethyl CH_3), 0.95 (d, 6H, leucine CH_3).

Preparation of Ethylmethoxyisoleucinyl Phosphorochloridate

L-Isoleucine methyl ester (1.72g, 11.9mmol) in anhydrous diethyl ether (5mL) was added dropwise with vigorous stirring to a solution of ethyl phosphorodichloridate (0.92g, 5.64mmol) in diethyl ether (10mL), at -40°C. The reaction was allowed to warm to ambient temperature, with stirring for 3 hours, and then filtered. The filtrate was concentrated in vacuo, to give the product as pale yellow oil (1.51g, 98%).

^{31}P nmr $\delta(CDCl_3)$ +11.86, +11.41.

^{1}H nmr $\delta(CDCl_3)$ 4.15 (m, 2H CH_2OP), 3.80 (m, 1H, CH^*), 3.70 (s, 3H, OCH_3), 3.40 (m, 1H, NH), 1.80 (m, 1H, isoleucine CH), 1.40 (t, 3H, ethyl CH_3), 1.30 (m, 2H, isoleucine CH_2), 0.95 (2xt, 6H, isoleucine CH_3).

EXAMPLE 1

Preparation of 3'-AZIDOTHYMIDINE-5'-(METHYLMETHOXYVALINYL)-PHOSPHATE (UCL 11)

3'-Azidothymidine (0.25g, 0.94 mmol) and ethylmethoxylvalinyl phosphorochloridate (0.92g, 3.74mmol, 4.0 eq) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylimidazole (0.6 mL, 7.48 mmol, 8.0 eq) for 16 hours at room temperature. T.L.C. (chloroform/methanol 9:1 v/v) revealed the reaction to be ca 80% complete, so the solvent was removed in vacuo and the white gummy residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (10 mL), then water (3x10 mL), then dried ($MgSO_4$) and evaporated in vacuo to a white gummy residue. This latter residue was dissolved in chloroform (10 mL) and then precipitated in light petroleum (400 mL). The white glassy precipitate was chromatographed on silica gel (30g) and the product, a white glass, was eluted with chloroform/methanol 95:5 v/v. Yield 0.13g, 30%. ^{31}P n.m.r. $\delta(CDCl_3)$ + 8.22 and + 8.11 ppm (3:2 ratio). ^{1}H nmr $\delta(CDCl_3)$ 8.90 (doublet, 1-H, N3-H), 7.40 and 7.30 (singlets, 1H, H-6), 6.20 and 6.0 (triplets, 3:2 ratio, 1-H, H-1'), 4.35 and 4.25 (multiplets, 1-H, H-4'), 4.20 (multiplet, 2-H, H-5'), 3.95 (multiplet, 1-H, H-3'), 3.60 - 3.70 (singlet - broad at base, 7-H, CH_3O, valine OCH_3 and valine *C-H), 3. 30 - 3.40 (quartet, 1-H, valine N-H), 2.40 and 2.20 (multiplets, 1H each, H-2'), 2.00 (multiplet, 1-H, valine Pr^1-H), 0.80 and

0.90 (doublets, 3-H each, valine CH_3).

^{13}C nmr $\delta(CDCl_3)$ 173.55 and 173. 43 (valine C=0), (diastereoisomers, 3:2 ratio, J=3.0 Hz), 163.59 (singlet,C-2), 150.17 and 150.12 (diastereoisomers, C-4, 3:2 ratio), 135.24 and 135.20 (diastereoisomers, C-6, 3:2 ratio), 111.84 and 111.31 (diastereoisomers, C-5, 3:2 ratio), 84.94 and 84.69 (diastereoisomers, C-1', 2:3 ratio), 82.38 and 82.28 (diastereoisomers, C-4', 3:2 ratio, J=7.0 Hz), 65.38 and 65.09 (diastereoisomers, C-5', 2:3 ratio, J=4.7 Hz), 60.32 and 60.16 (diastereoisomers, C-3', 2:3 ratio), 59.84 and 59.73 (diastereoisomers, valine asymmetric C, 2:3 ratio), 53.54 and 53.45 (diastereoisomers, CH_3O, 3:2 ratio, J=4.3 Hz), 52.29 (singlet, valine OCH_3), 37.47 and 37.43 (diastereoisomers, C-2', 3:2 ratio), 31.95 and 31.86 (diastereoisomers, valine isopropyl C, 3:2 ratio, J=6.7 Hz), 19.11 (singlet, valine CH_3), 17.21 and 17.15 (diastereoisomers, valine CH_3, 2:3 ratio), 12.44 and 12.33 (diastereoisomers, C-5-CH_3, 2:3 ratio).

$C_{17}H_{27}N_6O_8P$. $(H_2O)_{0.5}$ Requires C 42.24, H 5.84, N 17.38; Found C 42.43, H 5.78, N 17.14.

EXAMPLE 2

Preparation of 3'-AZIDOTHYMIDINE-5'-(ETHYLMETHOXYVALINYL)-PHOSPHATE (UCL 12,19,20)

3'-Azidothymidine (0.26g, 0.97mmol) and ethymethoxyvalinylphosphorochloridate (0.5g, 1.94 mmol, 2.0 eq) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylimidazole (0.31 mL, 3.88 mmol, 4.0 eq) for 16 hours at room temperature. T.L.C (chloroform/methanol 9:1 v/v) revealed the reaction to be ca 95% complete, so the solvent was removed in vacuo, and the white gummy residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (10mL), then water (3x10 mL), then dried ($MgSO_4$) and evaporated in vacuo to a white gummy

residue. This was dissolved in chloroform (10 mL), and precipitated with light petroleum (400 mL). The white glassy precipitate was chromatographed on silica gel (30g) and the product, a white glass, was eluted with chloroform/methanol 94:6 v/v. Yield 0.32g, 67%.

^{31}P nmr $\delta(CDCl_3)$ + 6.726 and + 6.872 ppm; ratio 3:2.

^{1}H nmr $\delta(CDCl_3)$ 8.50 (doublet 1H, N3-H), 7.45 and 7.35 (singlets, 3:2 ratio, 1H, H-6), 6.26 and 6.15 (triplets, 3:2 ratio, 1H, H-1'), 4.30 to 4.40 (multiplets, 3:2 ratio, 1H, H- 4'), 4.25 (multiplet, 2H, H-5'), 4.10 (multiplet, 2H, ethyl CH_2), 4.00 (multiplet, 1H, H-3'), 3.70 (singlet, broad at base, 4H, valinyl OCH_3 and *C-H), 3.20 to 3.30 (quartet, 1H, valinyl N-H), 2.40 and 2.20 (multiplets, 1H each, H-2'), 2.10 (multiplet, 1H, valine Pr^i-H), 1.90 (singlet, 3H, 5-CH_3), 1.30 (multiplet, 3H, ethyl CH_3), 0.80 and 0 90 (doublets, 3H each, valine CH_3).

^{13}C nmr $\delta(CDCl_3)$ 173.54 and 173.44 (valine C=O, 3:2 ratio, d, J=3.0 Hz), 163.70 (singlet, C2), 150.28 and 150.23 (C4, 3:2 ratio), 135.14 and 135.11 (C6, 3:2 ratio), 111.46 and 111.31 (C5, 3:2 ratio), 84.90 and 84. 64 (C-1', 2:3 ratio), 82.44, 82.36 (C-4', 2:3 ratio, J=7.2 Hz), 65.45 and 65.19 (C- 5', 2:3 ratio, J=5.0 Hz), 63.15 and 63.10 (ethyl CH_2, 3:2 ratio, d, J=5.0 Hz), 60.38 and 60.34 (C-3', 2:3 ratio), 59.81 and 59.77 (valine asymmetric C, 2:3 ratio), 52.17 (singlet, valine OCH_3), 37.44 and 37.38 (C-2', 3:2), 31.93 and 31.86 (valine isopropyl C, 3:2 ratio, d, J=7.0 Hz), 19.06 and 18.99 (valine CH_3, 3:2 ratio), 17.26 and 17.23 (valine CH_3, 2:3 ratio), 16.16 and 16.10 (ethyl CH_3, 3:2 ratio), 12.45 and 12.37 (5-CH_3, 2:3 ratio). $C_{16}H_{29}N_6O_8P$: requires C 44.26, H 5.98, N 17.21, P 6.34; Found C 44.23, H 6.17, N 16.84, P 6.33.

The mixture of diastereomers (UCL 12) was partially separated to give fast and slow running fractions (UCL 19 and UCL 20 respectively). Partial separation was accomplished by HPLC, employing a Waters system using a 25cm x 4.6mm Partisil 5 silica column, and a mobile phase of 90% ethyl acetate/10% petroleum spirit, with a flow rate of

2.0cm^3/min. Detection was by UV at 254nm.

EXAMPLE 3

Preparation of 3'-AZIDOTHYMIDINE (PROPYLMETHOXYVALINYL) PHOSPHATE (UCL 13)

3'-Azidothymidine (0.4g, 1.50 mmol) and propylmethoxyvalinylphosphorochloridate (0.82, 3.02 mmol, 2.0 eq) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylimidazole (0.48 mL, 6.00 mmol, 4.0 eq) for 16 hours at room temperature. T.L.C. (chloroform/methanol 9:1 v/v) revealed the reaction to be ca 90% complete, so the solvent was removed in vacuo, and the white gummy residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (10 mL), then water (3x10 mL), dried ($MgSO_4$) and then evaporated in vacuo to a white gummy residue. This latter residue was dissolved in chloroform (10 mL) then precipitated in light petroleum (500 mL). The white precipitate was then chromatographed on silica gel (30g) and the product, a white glass, eluted with chlorofrom/methanol 96:4 v/v.

Yield 0.39g, 52%. ^{31}P n.m.r. $\delta(CDCl_3)$ + 6.94 and + 6.74 ppm (3:2 ratio). ^1H n.m.r. $\delta(CDCl_3)$ 8.50 (doublet, 1H, N3-H), 7.40 and 7.30 (singlets, 3:2 ratio, 1H, H-6), 6.20 and 6.10 (triplets, 3:2 ratio, 1H, H-1'), 4.35 and 4.25 (multiplets, 3:2 ratio, 1H, H-4'), 4.20 and 4.10 (multiplets, 3:2 ratio, 2H, H-5'), 3.85 to 4.00 (multiplets, 3H, propyl CH_2O and H-3'), 3.65 (singlet, 4H, valine OCH_3 and *C-H), 3.25 (quartet, 1H, valine N-H), 2.40 and 2.20 (multiplets, 1H each, H-2'), 2.00 (multiplet, 1H, valine isopropyl C-H), 1.90 (singlet, 3H, 5-CH_3), 1.60 (multiplet, 2H, propyl CH_2), 1.90 (m, 3H, propyl CH_3), 1.80 (m, 6H, valine CH_3). ^{13}C $\delta(CDCl_3)$, 173.54 and 173.44 (diastereoisomers, valine C=0, 3:2 ratio, J=3.0 Hz), 163.67 (singlet, C-2), 150.25 and 150.20 (diastereoisomers, C-4, 3:2 ratio), 135.17 and 135.14 (diastereoisomers, C-6, 3:2 ratio), 111.48 and 111.35

(diastereoisomers, C-5, 3:2 ratio), 84.90 and 84.64 (diastereoisomers, C-1', 2:3 ratio), 82.42 and 82.31 (diastereoisomers, C-4', 3:2 ratio, J=6.8 Hz), 68.58 and 68.51 (diastereoisomers, propyl CH_2O, 2:3 ratio, J=5.1 Hz), 65.29 and 65.18 (diastereosiomers, C-5', 2:3 ratio, J=5.1 Hz), 60.43 (singlet, C-3'), 59.81 and 59.75 (diastereoisomers, valine asymmetric C, 2:3 ratio), 52.18 (singlet, valine OCH_3), 37.44 and 37.37 (diastereoisomers, C- 2', 3:2 ratio), 32.01 and 31.95 (diastereoisomers, valine isopropyl C, 2:3 ratio, J=6.5 Hz), 23.65 and 23.58 (diastereoisomers, propyl CH_2, 2:3 ratio), 19.09 and 19.02 (diastereoisomers, valine CH_3, 3:2 ratio), 17.28 and 17.21 (diastereoisomers, valine CH_3, 2:3 ratio), 12.48 and 12.40 (diastereoisomers, C-5-CH_3, 2:3 ratio), 9.97 (singlet, propyl CH_3). $C_{19}H_{31}N_6O_8P.(H_2O)_{0.25}$ Requires C 45.01, H 6.62, N 16.58, P 6.11. Found C 44.94, H 6.19, N 16.51, P 6.21.

EXAMPLE 4

Preparation of 3'-AZIDOTHYMIDINE (BUTYLMETHOXYVALINYL) PHOSPHATE (UCL 14)

3'-Azidothymidine (0.34g, 1.28 mmol) and butylmethoxyvalinyl phosphorochloridate (0.73g, 2.56 mmol, 2.0 eq) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylimidazole (0.4 mL, 5.08 mmol, 4.0 eq) for 16 hours at room temperature. T.L.C. (chloroform/methanol 9:1 v/v revealed the reaction to be ca 95% complete, and so the solvent was removed in vacuo and the white gummy residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (10 mL), then water (3x10) mL), dried ($MgSO_4$) and then evaporated in vacuo to a white gummy residue. This latter residue was dissolved in chloroform (10 mL) then precipitated in light petroleum (500 mL). The white glassy precipitate was then chromatographed on silica gel (30g) and the product, a white glass, eluted with chloroform/methanol 96:4 v/v.
Yield 0.40g, 61% ^{31}P n.m.r. $\delta(CDCl_3)$ + 6.96 and + 6.77 (3:2

ratio). ^{1}H n.m.r. $\delta(CDCl_3)$ 8.70 (doublet, 1H N3-H), 7.40 and 7.30 (singlets, 3:2 ratio, 1H, H-6), 6.25 and 6.15 (triplets, 3:2 ratio, 1H, H-1') 4.30 to 4.40 (multipets, 3:2 ratio, 1H, H-4'), 4.20 (multiplet, 2H, H-5'), 4.00 (multiplet, 3H, butyl CH_2O and H-3'), 3.70 (singlet, 4H, valine OCH_3 and *C-H), 3.30 (multiplet, 1H, valine N-H), 2.40 and 2.20 (multiplets, 1H each, H-2'), 2.00 (multiplet, 1H, valine Pr^i-H), 1.90 (singlet, 3H, 5-CH_3), 1.60 (multiplet, 2H, butyl CH_2), 1.35 (multiplet, 2H, butyl CH_2), 0.80 to 1.00 (multiplet, 9H, butyl and valinyl CH_3). ^{13}Cnmr $\delta(CDCl_3)$ 173.54 and 173.44 (diastereoisomers, valine C=O, 3:2 ratio, J=3.0 Hz), 163.68 (singlet, C-2), 150.26 and 150.21 (diastereoisomers, C-4, 3:2 ratio), 135.16 (singlet, C-6), 111.48 and 111.34 (diastereoisomers, C-5, 3:2 ratio), 3:2 ratio), 84.90 and 84.64 (diastereoisomers, C- 1', 2:3 ratio) 82.40 and 82.31 (diastereoisomers, C-4', 3:2 ratio, J=7.0Hz), 66.89 and 66.84 (diastereoisomers, butyl CH_2O, 3:2 ratio, J=5.2 Hz), 65.29 and 65.20 (diastereoisomers, C-5', 2:3 ratio, J=5.2 Hz), 60.4 (singlet, C-3'), 59.81 and 59.75 (diastereoisomers, valine asymmetric C, 2:3 ratio), 52.18 (singlet, valine OCH_3), 37.43 and 37.36 (diastereoisomers, C2', 3:2 ratio), 32.25 and 32.03 (diastereoisomers, butyl CH_2, 3:2 ratio, J=7.1 Hz), 31.95 and 31.87 (diastereoisomers, valine isopropyl C, 3:2 ratio, J=6.7 Hz), 19.05 and 19.01 (diastereoisomers, valine CH_3, 3:2 ratio), 18.66 (singlet, butyl CH_2), 17.28 and 17.22 (diastereoisomers, valine CH_3, 2:3 ratio), 13.56 (singlet, butyl CH_3), 12.47 and 12.39 (diastereoisomers, 5- CH_3, 2:3 ratio).

$C_{20}H_{33}N_6O_8P.$ $(H_2O)_{0.15}$ Require C 46.27, H 6.47, N 16.19, P 5.97. Found C 46.29, H 6.46, N 15.86, P 6.20.

EXAMPLE 5

Preparation of 3'-AZIDOTHYMIDINE-5'-(HEXYLMETHOXYVALINYL)-PHOSPHATE (UCL 15,16,17)

3'-Azidothymidine (0.44g, 1.34 mmol), and hexylmethoxyvalinylphosphorochloridate (1.22g, 4.03 mmol, 3.0 eq) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylmidazole (0.64 mL, 8.06 mmol 6.0 eq) for 16 hours at room temperature. T.L.C. (chloroform/methanol 9:1 v/v) revealed the reaction to be complete, so the solvent was removed in vacuo and the white gummy residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (10 mL), then water (3x10 mL), dried ($MgSO_4$) and then evaporated in vacuo to a white gummy residue. This latter residue was dissolved in chloroform (10 mL) and then precipitated in light petroleum (500 mL). The white glassy precipitate was then chromatographed on silica gel (40g) and the product eluted with chloroform/methanol 95:5 v/v.

The required fractions were split into three batches, the first five (UCL 15), middle three (UCL 16) and final four (UCL 17) and each batch was evaporated in vacuo to a white glassy residue, (0.5g, 75%). ^{31}P n.m.r. First batch ($CDCl_3$) + 8.50 and +8.80 ratio 1:5. Middle batch + 8.50 and + 8.80 ratio ca 2:3. Last batch + 8.50 and + 8.80 ratio ca 3:2.

^1H n.m.r. $\delta(CDCl_3)$ 8.55 (doublet, 1H, N3-H), 7.45 and 7.35 (singlets, 1:1 ratio, 1H, H-6), 6.25 and 6.15 (triplets, 1H H-1') 4.30 to 4.40 (multiplets, 1H, H-4'), 4.20 (multiplet, 2H, H-5'), 4.00 (multiplet, 2H, $HexCH_2O$ and H-3'), 3.70 (singlet, 4H, valine OCH_3 and *C-H), 3.30 (multiplet, 1H, valine N-H), 2.40 (multiplet, 1H, H-2'), 2.30 (multiplet, 1H, H-2'), 2.10 (multiplet, 1H valine Pr^1-H), 1.90 (singlet, 3H, 5-CH_3), 1.65 (multiplet, 4H, hexyl CH_2), 1.30 (multiplet, 6H, hexyl CH_2), 1.00 (triplet, 3H, hexyl CH_3),

0.90 (doublet, 6H, valine CH_3). ^{13}C nmr $\delta(CDCl_3)$ 173.46 and 173.38 (diastereoisomers, 1:1 ratio, valine C=O, J=3.1 Hz), 163.80 (singlet, C-2), 150.37 and 150.32 (diastereoisomers, 1:1 ratio, C-4), 135.10 (singlet, C-6), 111.4 and 111.28 (diastereoisomers, 1:1 ratio, C-5), 84.91 and 84.65 (diastereoisomers, 1:1 ratio, C-1'), 82.41 and 82.34 (diastereoisomers, 1:1 ratio, (C-4', J=5.0 Hz), 67.19 and 67.09 (diastereosiomers, 1:1 ratio, hexyl CH_2, J=4.1 Hz), 65.30 and 65.16 (diastereoisomers, 1:1 ratio, C-5', J=5.1 Hz), 60.44 (singlet, C-3'), 59.82 and 59.78 (diastereoisomers, 1:1 ratio, valine *C, J=4.7 Hz), 52.03 (singlet, valine OCH_3), 37.35 and 37.28 (diastereoiomers, 1:1 ratio, C- 2'),31.99 and 31.91 (diastereoisomers, 1:1 ratio, valine isopropyl C, J=6.4 Hz), 31.20 (singlet, hexyl CH_2), 30.21 and 30.15 (diastereoisomers, 1:1 ratio, hexyl CH_2), 25.04 (singlet, hexyl CH_2), 22.37 (singlet,hexyl CH_2), 18.96 and 18.89 (diastereoisomers, 1:1 ratio, valine CH_3), 17.31 and 17.25 (diastereoisomers, 1:1 ratio, valine CH_3), 13.81 (singlet, hexyl CH_3), 12.35 and 12.29 (diastereoisomers, 1:1 ratio, C5-CH_3).

$C_{22}H_{37}N_6O_8P$. $(H_2O)_{0.5}$ requires C 47.74, H 6.92, N 15.18, P 5.60; found C 48.04, H 6.65, N 14.85, P 5.83.

EXAMPLE 6

PREPARATION OF 3'-AZIDOTHYMIDINE-5'-(ETHYL-METHOXYPHENYLALANINYL)-PHOSPHATE (UCL 21)

3'-Azidothymidine (0.1g, 0.37 mmol) and ethyl-methoxyphenylalaninylphosphorochloridate (0.27g, 0.88 mmol, 2.35 eq) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylimidazole (0.14 mL, 1.76 mmol, 4.70 eq) at room temperature for 48 hours. T.L.C. (chloroform/methanol 9:1 v/v) revealed the reaction to be ca 90% complete, so it was concentrated in vacuo and the gummy residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate

solution (10mL) then water (3x10 mL), and then dried ($MgSO_4$) and evaporated in vacuo to a gum. This latter residue was precipitated in light petroleum (400 mL) from chlorofrom (10 mL). The gummy precipitate was then chromatographed in silica gel (15.0g), and the desired product, a white glass, eluted with chloroform/methanol 96:4 v/v. Yield 0.11g, (55%). ^{31}P n.m.r. $\delta(CDCl_3)$ + 8.65. ^{1}H n.m.r. $\delta(CDCl_3)$ 9.70 (doublet, 1H, N3-H), 7.40 and 7.30 (singlets, 3:2 ratio, 1H, H-6), 7.10 to 7.35 (multiplets, 5H, phenyl), 6.25 and 6.15 (triplets, 1H, H-1'), 4.30 (multiplet, 1H, H- 4'), 3.80 to 4.10 (multiplet, 4H, H-5' and ethoxy CH_2O), 3.60 to 3.80 (sharp singlet and multiplet, 5H, phenylalanine OCH_3, asymmetric C-H and N-H), 3.10 (doublet, 1H, phenylalanine CH_2), 2.90 (multiplet, 1H, phenylalanine CH_2), 2.40 (multiplet, 1H, H-2'), 2.20 (multiplet, 1H H-2'), 1.90 (singlet, 3H, C5-CH_3), 1.20 (triplet, 3H, ethoxy CH_3). $C_{22}H_{29}N_6O_8P$. H_2O requires C 47.65, H 5.64, N 15.16. Found C 48.11, H 5.35 N 14.73.

EXAMPLE 7

Preparation of 3'-AZIDOTHYMIDINE-5'-(ETHYL-METHOXYLALANINYL)-PHOSPHATE (UCL 22)

3'-Azidothymidine (0.20g, 0.75 mmol) and ethylmethoxyalaninylphosphorochloridate (0.60g, 2.62 mmol, 3.5 eq) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylimidazole (0.42 mL, 5.24 mmol, 7.0 eq) for 48 hours T.L.C. (chloroform/methanol 9:1 v/v) revealed the reaction to be complete. It was concentrated in vacuo and the gummy residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (10 mL), then water (3x10 mL) and then dried ($MgSO_4$) and evaporated in vacuo to a white gummy residue. This residue was then dissolved in chloroform (10mL) and precipitated in light petroleum (400 mL). The gummy precipitate was chromatographed on silica gel (40g) and the product, a white glass, eluted with

chloroform/methanol 96:4 v/v. Yield 0.32g, (93%). ^{31}P n.m.r. $\delta(CDCl_3)$ +5.73 and + 5.81 (ratio 4:3). ^{1}H n.m.r. $\delta(CDCl_3)$ 9.40 (doublet, 1H, N3-H), 7.40 and 7.30 (singlets, 1H, H-6), 6.20 and 6.10 (triplets, 3:2 ratio, 1H, H-1'), 4.40 and 4.30 (multiplets, 3:2 ratio, 1H, H-4'), 4.10 to 4.25 (multiplet, 2H, H-5'), 4.00 (multiplet, 2H, ethoxy CH_2), 3.90 (multiplet, 1H, H-3'), 3.85 (multiplet, 1H, alanine N-H), 3.50 to 3.70 (singlet, 4H alanine *C-H and OCH_3), 2.40 (multiplet, 1H, H-2'), 2.20 (multiplet, 1H, H-2'), 1.85 (singlet, 3H, 5-CH_3), 1.40 (doublet, 3H, alanine CH_3). ^{13}C n.m.r. $\delta(CDCl_3)$ 174.30 and 174.24 (diastereoisomers, 4:3 ratio, alanine C=O, J=6.0 Hz), 163.77 (singlet, C-2), 150.25 and 150.30 (diastereoisomers, 3:4 ratio, C-4), 135.41 and 135.09 (diastereoisomers, 4:3 ratio, C-6), 111.44 and 111.31 (diastereoisomers, 4:3 ratio, C-5), 84.90 and 84.60 (diastereosiomers, 4:3 ratio, C-1'), 82.40 and 82.32 (diastereoisomers, 3:4 ratio, C-4', J=7.6 Hz), 65.19 and 65.01 (diastereoisomers, 3:4 ratio, C-5', J=5.0 Hz), 63.11 and 62.98 (diastereosiomers, 4:3 ratio, ethyl CH_2 J=5.0 Hz), 60.37 and 60.29 (diastereoisomers, 3:4 ratio, C-3'), 52:48 (singlet, alanine OCH_3), 50.09 and 49.95 (diastereoisomers 4:3 ratio, alanine asymmetric C), 37.36 and 37.39 (diastereoisomers 4:3 ratio, C-2') 21.07 and 20.93 (diastereoisomers, 3:4 ratio, alanine CH_3), 16.12 and 16.06 (diastereoisomers, 4:3 ratio, ethyl CH_3, J=5.4 Hz), 12.39 and 12.34 (diastereoisomers, 3:4 ratio, 5-CH_3). $C_{16}H_{25}N_6O_8P.H_2O$ requires C 40.17, H 5.69, N 17.57, P 6.47. Found C 40.13, H 5.56, N 17.72, P 6.75.

EXAMPLE 8

PREPARATION OF 3'-AZIDOTHYMIDINE-5'-(ETHYL-METHOXYLEUCINYL)-PHOSPHATE (UCL 23)

3'-Azidothymidine (0.2g, 0.75 mmol) and ethylmethoxy-leucinylphosphorochloridate (0.72g, 2.26 mmol, 3.5eq) were stirred together in anhydrous tetrahydrofuran (10 mL) in the

presence of N-methylimidazole (0.42 mL, 5.24 mmol, 7.0 eq) at room temperature for 24 hours. T.L.C. (chloroform/methanol 9:1 v/v) revealed the reaction to be ca 90% complete, so the solvent was removed in vacuo and the white gummy residue dissolved in chlorofrom (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (20 mL), then water (3 x 15 mL), then dried ($MgSO_4$) and evaporated in vacuo to a white gummy residue, which was precipitated in light petroleum (400 mL) from chlorofrom (10 mL). The gummy preciptitate was chromatographed on silica gel (40g) and the required product eluted with chloroform/methanol 96:4 v/v, and isolated as a white glass.

Yield 0.18g, (52%). ^{31}P n.m.r. $\delta(CDCl_3)$ + 8.65. ^{1}H n.m.r. $\delta(CDCl_3)$ 9.40 (doublet, 1H N3-H), 7.50 and 7.40 (singlets 3:1 ratio, 1H, H-6), 6.30 and 6.20 (triplets, 1H, H-1'), 4.30 and 4.20 (multiplets, 1H, H-4'), 4.25 (multiplet, 1H H-3'), 4.10 to 4.20 (multiplet, 3H, H-3' and ethoxy CH_2), 4.05 (multiplet, 2H, H-5'), 3.90 (multiplet, 1H, *C-H), 3.70 (singlet, 3H, leucine OCH_3), 3.50 (multiplet, 1H, leucine N-H), 2.40 (multiplet, 1H, H-2'), 2.30 (multiplet, 1H, H-2'), 1.90 (singlet, 3H, 5-CH_3), 1.75 (multiplet, 1H, leucine CH_2), 1.60 (multiplet, 1H, leucine CH_2), 1.50 (multiplet, 1H, leucine Pr^i-H), 1.30 (multiplet, 3H, ethoxy CH_3), 0.90 (doublet, 6H, leucine CH_3).

^{13}C n.m.r. $\delta(CDCl_3)$ 174.54 and 174.43 (diastereoisomers, 6:4 ratio, leucine C=O, J=3.0 Hz), 163.99 (singlet, C-2), 150.42 and 150.37 (diastereoisomers, 6:4 ratio, C-4), 135.09 (singlet, C-6), 111.30 and 111.16 (diastereoisomers 6:4 ratio, C-5) 84.65 and 84.40 (diastereosiomers, 4:6 ratio C-1') 82.26 and 82.16 (diastereoisomers, 4:6 ratio, C-4', J=7.0 Hz), 65.09 and 64.99 (diasteroisomers, 4:6 ratio, C-5', J=5.4 Hz), 62.90 (singlet, ethyl CH_2O), 60.29 and 60.24 (diastereoisomers, 4:6 ratio, C-3'), 52.74 (singlet, OMe), 52.72 and 52.12 (diastereoisomers, 6:4 ratio, leucine C-H, J=3.0 Hz), 43.42 and 43.28 (diastereoisomers, 4:6 ratio,

leucine CH_2, J=9.1 Hz), 37.23 and 37.15 (diastereoisomers, 6:4 ratio, C-2'), 24.33 and 24.28 (diastereoisomers, 6:4 ratio, leucine Pr^i-H), 22.53 (singlet, leucine CH_3), 21.51 and 21.48 (diastereoisomers, 4:6 ratio, leucine CH_3), 15.99 and 15.93 (diastereoisomers, 4:6 ratio, ethyl CH_3), 12.31 and 12.23 (diastereoisomers, 4:6 ratio, 5-CH_3). $C_{19}H_{31}N_6O_8P.(H_2O)_{1.25}$ requires C 43.47, H 6.43, N 16.01, P 5.90. Found C 43.12, H 6.03, N 15.72, P 5.45.

EXAMPLE 9

PREPARATION OF 3'-AZIDOTHYMIDINE-5'-(ETHYL-METHOXYISOLEUCINYL)-PHOSPHATE (UCL 24)

3'-Azidothymidine (0.15g, 0.56 mmol) and ethyl-methoxyisoleucinylphosphorochloridate (0.68g, 2.50 mmol, 4.47 eq.) were stirred together in anhydrous tetrahydrofuran (5 mL) in the presence of N-methylimidazole (0.4 mL, 0.50 mmol, 8.93 eq) for 16 hours at room temperature. T.L.C. (chloroform/methanol 9:1 v/v) revealed the reaction to be complete, so the solvent was removed in vacuo, and the residue dissolved in chloroform (30 mL). The organic solution was washed with saturated sodium bicarbonate solution (20 mL), then water (3x10 mL), dried ($MgSO_4$) and then evaporated in vacuo to a yellow gummy residue. This latter residue was precipitated in light petroleum (400 mL) from chloroform (10 mL). The gummy precipitate was chromatographed on silica gel (30 g) and the desired product, a white glass, eluted with chloroform/methanol 94:6 v/v. Yield 0.18g, (64%). ^{31}P n.m.r. $\delta(CDCl_3)$ + 9.68 and + 9.55 (3:2). ^1H n.m.r. $\delta(CDCl_3)$ 8.90 (doublet, 1H, N3-H), 7.50 and 7.40 (singlets, 3:2 ratio, 1H, H-6), 6.30 and 6.20 (triplets, 1H, H-1'), 4.40 and 4.30 (multiplets, 1H, H-4'), 4.25 (multiplet, 1H, H-5'), 4.10 to 4.20 (multiplet, 3H, ethoxyCH_2 and H-3'), 4.05 (multiplet, 1H, H-5'), 3.80 (singlet, 4H, isoleucinyl C-H and OCH_3), 3.40 (multiplet, 1H, isoleucinyl N-H), 2.45 (multiplet, 1H, H-2'), 2.25

(multiplet, 1H,H-2'), 2.00 (singlet, 3H, 5-CH_3), 1.80 (broad multiplet, 2H, isoleucine-CH_2), 1.40 (multiplet, 1H isoleucinyl Pr^i-H), 1.30 (triplet, 3H, ethoxy CH_3), 0.90 (multiplet, 6H, isoleucinyl CH_3). ^{13}C n.m.r. $\delta(CDCl_3)$ 173.51 and 173.41 (diastereoisomers, 4:3 ratio, ileu C=O, J=3.0 Hz), 163.89 (singlet, C-2), 150.37 and 150.33 (diastereosiomers, 4:3 ratio, C-4), 135.16 and 135.14 (diastereoisomers, 4:3 ratio, C-6, ratio C-6), 111.42 and 111.28 (diastereoisomers, 4:3 ratio, C-5), 84.82 and 84.55 (diastereoisomers, 3:4 ratio, C-1') 82.35 and 82.25 (diastereoisomers, 4:3 ratio, C-4', J=5.8 Hz), 65.22 and 65.05 (diastereoisomers, 3:4 ratio, C-5', J=5.1 Hz), 63.09 and 63.04 (diastereoisomers, ethyl CH_2O, J=5.2 Hz), 60.34 and 60.29 (diastereoisomers, 3:4 ratio, C-3'), 58.93 and 58.90 (diastereoisomers, 4:3 ratio, ileu C*, J=3.6 Hz), 52.08 (singlet, ileu OCH_3), 38.92 and 38.83 (diastereoisomers, 3:4 ratio, ileu, C-H), 37.37 and 37.31 (diastereoisomers, 4:3 ratio, C-2'), 24.55 (singlet, ileu CH_2), 16.08 and 16.04 (diastereoisomers, 4:3 ratio, ethyl CH_3, J=4.5 Hz), 15.46 (singlet, ileu CH_3) 15.38 (singlet, ileu CH_3), 12.41 and 12.34 (diastereoisomers 3:4 ratio, C5-CH_3). $C_{19}H_{31}N_6O_8P$. $(H_2O)_{1.35}$ requires C 43.32, H 6.45, N 15.95. Found C 43.10, H 6.27, N 16.23.

Example 10

Preparation of 3'-Azidothymidine-5'-(2,2,2-trichloroethyl methoxyalaninyl) phosphate,(UCL 89)

2,2,2-Trichloroethyl methoxyalaninyl phosphorochloridate (0.37g, 1.12mmol) was added to a solution of AZT (0.10g, 0.37mmol) in anhydrous THF (5ml) containing N-methylimidazole (0.42 ml, 5.24 mmol), and the mixture stirred for 16h at ambient temperature. The solvent was removed under reduced pressure, and the residue dissolved in chloroform (30ml), and extracted with saturated sodium bicarbonate solution (15ml), and then with water (2x15ml).

The organic phase was dried over magnesium sulphate, and concentrated under reduced pressure. The residue was precipitated from chloroform (10ml), by the addition of petroleum ether (400ml; bp 30-40°C). The product was then purified by flash column chromatography on silica gel, using 4% methanol in chloroform as eluant. Pooling and evaporation of appropriate fractions gave the product (0.21g, 99%).

^{31}P nmr $\delta(CDCl_3)$ +4.73, +4.56

^{1}H nmr $\delta(CDCl_3)$ 9.00(1H, d, NH), 7.31(1H, s, H6), 7.30/7.20(1H, d, H6), 6.15/6.05(1H, m, H1'), 4.50(2H, m, H5'), 4.35(1H, m, H3'), 4.25(2H, m, CH_2OP), 3.90-4.00(2H, m, H4', ala CH*), 3.80(1H, m, ala NH), 3.60(3H, s, OCH_3), 2.40(1H, m, H2'), 2.20(1H, m, H2') 1.90(3H, s, CH_3), 1.40(3H, d, ala CH_3).

^{13}C nmr $\delta(CDCl_3)$ 174.05/174.01(3:4, ala C=O, d, J=7.0Hz), 163.85 (C2), 150.38/150.32(3:4, C4), 135.61/135.45(4:3, C6), 111.63/111.51(3:4, C5), 95.30(CCl_3, m), 85.60/85.14(4:3, C1'), 82.25/82.18(3:4, C4', d, J=3.0Hz), 76.35/76.20(4:3, CH_2OP, d, J=3.3Hz), 66.09/65.90(3:4, C5', d, J=6.7Hz), 60.54/60.39(3:4, C3'), 52.77 (OCH_3), 50.19/50.09(4:3, ala CH*), 37.25(C2'), 20.89/20.84(4:3, ala Me, d, J=3.2Hz), 12.57(5-CH_3).

HPLC: Using a 50+250x4.6mm Spherisorb OD52 (5μm) column, and a mobile phase of water (A) and 5% water in acetonitrile (B), with 80% (A) at 0-10 min. and then a linear gradient to 20% (A) at 30 min., with a flow rate of 1.0 cm^3/min. Detection was by UV, at 254nm with a retention time of 25.36 min., and no AZT observed.

EXAMPLE 11

3'-Azido-3'-deoxythmyidine-5'-(ethyl propylamino) phosphate (UCL38)

Ethyl propylamino phosphorochloridate (0.35g, 1.87mmol) was added to a solution of AZT (0.20g, 0.74mmol) in anhydrous THF (5mL) containing N-methylimidazole (0.30mL, 3.75mmol), and the mixture stirred for 16h at ambient temperature. The solvent was removed under reduced pressure, and the residue dissolved in chloroform (30mL), extracted with saturated sodium bicarbonate solution (15mL), and then with water (2x15mL). The organic phase was dried over magnesium sulphate, and concentrated under reduced pressure. The residue was precipitated from chloroform (10mL), by the addition of petroleum ether (400mL; bp 30-40). The product was then purified by flash column chromatography on silica gel, using 4% methanol in chloroform as eluant. Pooling and evaporation of appropriate fractions gave the product (0.21g, 68%). δ_p +9.81; δ_H (starred peaks are duplicated due to diastereoisomers) 9.10* (1H, s, N^3H), 7.35* (1H, s, H6), 6.15* (1H, t, H1'), 4.35 (1H, m, H3'), 4.20 (2H, m, H5'), 4.00-4.10 (3H, m, $POCH_2$, H4'), 3.40 (1H, m, NH), 2.80 (2H, m, $NHCH_2$), 2.40 (1H, m, H2'), 2.30 (1H, m, H2'), 1.90 (3H, s, 5-Me), 1.50 (2H, m, $NHCH_2CH_2$ 1.40 (3H, t, CH_3CH_2), 0.80 (3H, t, $NHCH_2CH_2CH_3$).

The compounds UCL 11 to UCL 17, UCL 19 to UCL 24, UCL 38 and UCL 89 were evaluated for anti-HIV activity in the following in vitro assays.

Primary Testing

1. 10 TCD50 HTLV III (RF) is added to the total number of cells required (10^7 - 10^8) and absorbed to the cells for 90 Min. at 37°C.

2. Cells are washed three times in PBSA to remove

unabsorbed virus and resuspended in the required volume of growth medium.

3. The cells ($2x10^5$/1.5ml) are then cultured in 6 ml tubes with drugs at two concentrations (100 and 1 μM) for 72h.

4. 200 μl of tissue culture supernatant from each sample is assayed for HIV antigen using a commercial ELISA.

5. Controls: (I) untreated infected cells;
(II) infected cells treated with AZT/ddC etc.

Secondary Evaluation (Titration)

1 and 2. (absorption and washing).

3. cells (2x105/1.5ml) are then cultured in 6 ml tubes with drugs at half log dilutions (10 - 0.001 μM) for 72h.

4. assayed for HIV by ELISA.

Toxicity Assay

This procedure is carried out simultaneously with the secondary evaluation of active compounds.

1. cells (2x105/1.5ml) are cultured in 6 ml tubes with drugs only at half log dilutions (100 - 0.01 μM) for 72H.

2. Cells are washed with PBSA and resuspended with 14C-protein hydrolysate in 100 μl and incubated overnight.

3. The cells are harvested, washed and ^{14}C incorporation

measured.

The assay results are summarised in Table 1 in which IC_{50} (μM) for each compound is the micromolar concentration of that compound required to inhibit HIV antigen formation by 50%. The results clearly show that the compounds UCL 11 to UCL 17, UCL 19 to UCL 24 and UCL 89 are effective in vitro inhibitors of HIV, even at concentrations of less than 100 μM. No assessment of inhibition of HIV antigen formation was performed at concentrations of the compounds above 100μl.

TABLE 1

UCL No.	Y	Z	X	IC_{50} (μM)
UCL 89	TCEO	MeAlaNH	N3	0.09
UCL 11	MeO	MeValNH	N3	3
UCL 14	BuO	MeValNH	N3	3
UCL 19	EtO(F)	MeValNH	N3	3
UCL 22	EtO	MeAlaNH	N3	3
UCL 12	EtO	MeValNH	N3	3
UCL 13	PrO	MeValNH	N3	10
UCL 16	HexO(M)	MeValNH	N3	10
UCL 17	HexO(S)	MeValNH	N3	10
UCL 21	EtO	MePheNH	N3	10
UCL 15	HexO(F)	MeValNH	N3	30
UCL 20	EtO(S)	MeValNH	N3	30
UCL 23	EtO	MeLueNH	N3	30
UCL 24	EtO	MeIleNH	N3	100
UCL 38	EtO	PrNH	N3	>100

(TCEO is 2,2,2-trichloroethoxy)

The invention is described in the foregoing description by way of example only. It will be appreciated by a man skilled in the art that many modifications of detail may be made without departing from the scope of the invention.

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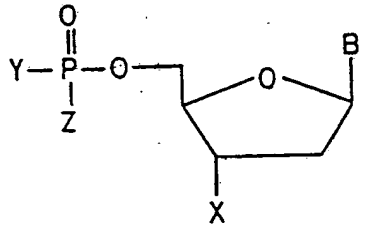
CLAIMS

1. A nucleoside analogue of the formula:



where B = an organic base
X = -H or $-N_3$
Z = $-NR^1R^2$, and
Y = $-OR^3$ or NR^4R^5

wherein R^1, R^2, R^3, R^4 and R^5 are the same or different and are selected from -H, alkyl, aryl, acyl substituted alkyl, substituted aryl and substituted acyl groups.

2. A nucleoside analogue according to Claim 1 wherein

Y = $-OR^3$

3. A nucleoside analogue according to Claim 1 or 2 wherein

R^1 = -H
R^2 = $CHR^6CO_2R^7$

where R^6 and R^7 are the same or different and are selected from H, alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups.

4. A nucleoside analogue according to any one of Claims

1 to 3 wherein

R^1 = -H,

R^2 = $-CHR^6CO_2Me$,

Y = OR^3,

R^6 = $-CHMe_2$, $-CH_2Ph$, -Me, $-CH_2CHMe_2$, $-CHMeCH_2Me$,

and

R^3 = Me, Et, Pr, Bu, Hex, 2,2,2-trichoroethyl.

5. A nucleoside analogue according to Claim 4 wherein the compound is;

3' - azidothymidine - 5' - (methylmethoxyvalinyl)-phosphate;

3' - azidothymidine - 5' - (ethylmethoxyvalinyl)- phosphate;

3' - azidothymidine - 5' - (propylmethoxyvalinyl)-phosphate

3' - azidothymidine - 5' - (butylmethoxyvalinyl)- phosphate;

3' - azidothymidine - 5' - (hexylmethoxyvalinyl)- phosphate;

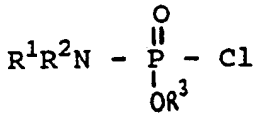
3' - azidothymidine - 5' - (ethylmethoxyalaninyl)-phosphate;

3' - azidothymidine - 5' - (ethylmethoxyphenylalaninyl)-phosphate;

3' - azidothymidine - 5'- (ethylmethoxyleucinyl)- phosphate;

3' - azidothymidine - 5' - (ethylmethoxyisoleucinyl)-phosphate; or 3'-azidothymidine-5'-(2,2,2-trichloroethyl methoxyalaninyl) phosphate.

6. A chemical compound of the formula



where R^1 - -H

R^2 = $-CH^6CO_2R^7$

R^3, R^6 and R^7 are the same or different and are selected from -H, alkyl, aryl, acyl, substituted alkyl, substituted aryl and substituted acyl groups.

7. A chemical compound according to Claim 6 wherein the compound is methylmethoxyvalinyl phosphorochloridate, ethylmethoxyvalinyl phosphorochloridate, propylmethoxyvalinyl phosphorochloridate, butylmethoxyvalinyl phosphorochloridate, hexylmethoxyvalinyl phosphorochloridate, ethylmethoxyalaninyl phosphorochloridate, ethylmethoxyphenylalaninyl phosphorochloridate, ethylmethoxyleucinyl phosphorochloridate, ethylmethoxyisoleucinyl phosphorochloridate, 2,2,2-trichloroethyl methoxyalaninyl phosphorochloridate.

8. A pharmaceutical composition comprising a nucleoside analogue according to any one of Claims 1 to 5 in association with a pharmaceutically acceptable excipient.

9. A nucleoside analogue according to any one of Claims 1 to 5 in a form suitable for parenteral administration.

10. A nucleoside analogue according to any one of Claims 1 to 5 for use as a pharmaceutical.

11. A process for the preparation of a pharmaceutical composition comprising bringing a nucleoside analogue according to any one of Claims 1 to 5 in association with a pharmaceutically acceptable excipient.

12. A method of treatment comprising the administration, to a human or animal in need of such treatment, of an effective amount of a nucleoside analogue according to any one of Claims 1 to 5.

13. Use of a nucleoside analogue according to any one of claims 1 to 5 for the manufacture of a medicament for the

treatment of a viral infection.

14. A pharmaceutically acceptable salt or addition compound of a nucleoside analogue according to any one of Claims 1 to 5.